

0590

RECEIVED
JUL 10 2002
TECH CENTER 1600/2900
8-102
P.2.

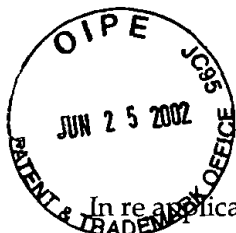
FIRST CLASS MAIL CERTIFICATE

I hereby certify that this document is being deposited with the United States Postal Service on this date as first class mail addressed to: Commissioner of Patents, United States Patent and Trademark Office, Washington, D.C. 20231.

Bernadette B. Fahey
Bernadette B. Fahey

June 17, 2002
Date

Att. Docket No. REG 780D



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of	:	Murphy, et al.
USSN	:	10/076,840
Filed	:	February 15, 2002
For	:	METHODS OF MODIFYING EUKARYOTIC CELLS
Examiner	:	Not Yet Known
Group	:	Not Yet Known

June 17, 2002

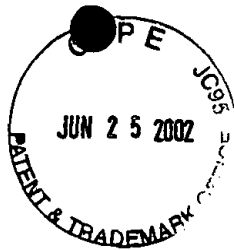
Commissioner for Patents
U.S. Patent and Trademark Office
Washington, D.C. 20231

TRANSMITTAL OF INFORMATION DISCLOSURE STATEMENT
UNDER 37 C.F.R. § 1.97(c) AND 1.98

SIR:

Submitted herewith is PTO Form 1449 to make of record those references of which Applicant is aware that may be pertinent to an examination of the captioned patent application on the merits. Copies of the listed references without an asterisk are enclosed, Copies of references with an asterisk may be found in parent case USSN 09/732,234.

Att. Dkt. No. REG 780D
USSN 10/076,840
Transmittal of IDS
Page 2



No fee is deemed necessary for filing this paper. However, if any fee is required, the Commissioner is hereby authorized to charge any such fee to Deposit Account No. 18-0650.

Respectfully submitted,

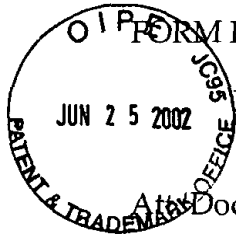
A handwritten signature in cursive script, reading "Linda O. Palladino".

Linda O. Palladino
Reg. No. 45,636
Patent Agent for Applicants
Gail M. Kempler
Reg. No. 32,143
Joseph M. Sorrentino
Reg. No. 32,598
Laura J. Fischer
Reg. No. 50,420
Attorneys for Applicants
Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, New York 10591
(914) 345-7400

RECEIVED

JUL 10 2002

TECH CENTER 1600/2900



FORM PTO-1449

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

Attorney Docket No.: : REG 780D
 USSN : 10/076,840
 Applicant : Murphy, et al.
 Date Filed : February 15, 2002
 For : METHODS OF MODIFYING
 EUKARYOTIC CELLS
 Examiner : Not Yet Known
 Group Art Unit : Not Yet Known
 June 17, 2002

U.S. PATENT DOCUMENTS

<u>Examiner Initials</u>	<u>Patent Number</u>	<u>Patent Date</u>	<u>Name</u>	<u>Class/ Subclass</u>	<u>Filing Date</u>
_____	* <u>5,789,215</u>	<u>08/04/98</u>	<u>Berns, et al.</u>	_____	_____
_____	* <u>5,436,149</u>	<u>07/25/95</u>	<u>Barnes, W.</u>	_____	_____

FOREIGN PATENT DOCUMENTS

<u>Examiner Initials</u>	<u>Document Number</u>	<u>Date</u>	<u>Country</u>	<u>Class/ Subclass</u>	<u>Translation</u> <u>Yes</u> <u>No</u>	
_____	<u>WO94/02602</u>	<u>02/03/94</u>	<u>PCT</u>	<u>C12N 15/00</u>	_____	_____

OTHER DOCUMENTS

**Examiner
Initials**

- _____ *NATURE, Vol. 317, 1985, Smithies, O., et al., "Insertion of DNA sequences into the human chromosomal β -globin locus by homologous recombination," pp. 230-234.
- _____ *CELL, Vol. 51, 1987, Thomas, K.R., and Capecchi, M.R., "Site-Directed Mutagenesis by Gene Targeting in Mouse Embryo-Derived Stem Cells," pp. 503-512.
- _____ *PROC. NATL. ACAD. SCI. USA, Vol. 86, 1989, Koller, B.H., et al., "Germ-line transmission of a planned alteration made in a hypoxanthine phosphoribosyltransferase gene by homologous recombination in embryonic stem cells," pp. 8927-8931.
- _____ *SCIENCE, Vol. 254, 1991, Kuhn, R., et al., "Generation and Analysis of Interleukin-4 Deficient Mice," pp. 707-710
- _____ *NATURE, Vol. 346, 1990, Thomas, K.R., and Capecchi, M.R., "Targeted disruption of the murine *int-1* proto-oncogene resulting in severe abnormalities in midbrain and cerebellar development," pp. 847-850.
- _____ *SCIENCE, Vol. 246, 1989, Schwartzberg, P.L., et al., "Germ-line Transmission of *c-abl* Mutation produced by Targeted Gene Disruption in ES Cells," pp. 799-803.

*NATURE, Vol. 330, 1987, Doetschman, T., et al., "Targetted correction of a mutant HPRT gene in mouse embryonic stem cells," pp. 576-578.

*CELL, Vol. 56, 1989, Thompson, S., et al., "Germ Line Transmission and Expression of a Corrected HPRT Gene Produced by Gene Targeting in Embryonic stem Cells," pp. 313-321.

*NATURE, Vol. 345, 1990, DeChiara, T.M., et al., "A growth-deficiency phenotype in heterozygous mice carrying an insulin-like growth factor II gene disrupted by targeting," pp. 78-80.

*NATURE, Vol. 369, 1994, Cheng, S., et al., "Long PCR," pp. 684-685.

*PCR METHODS AND APPLICATIONS, 1994, Foord, O.S., and Rose, E.A., "Long-distance PCR," pp. 3:S149-S161.

*NUCLEIC ACIDS RESEARCH, Vol. 20 No. 3, 1992, Ponce, M.R., and Micol, J.L., "PCR amplification of long DNA fragments," p.623.

*GENE TARGETING-A PRACTICAL APPROACH, 2nd Ed., 2000, Edited by Joyner, A.L., Hasty, P. et al., Chapter 1 "Gene targeting, principles, and practice in mammalian cells," pp. 1-35.

*MOLECULAR AND CELLULAR BIOLOGY, Vol. 12 No. 8, 1992, Deng, C., and Capecchi, M.R., "Reexamination of Gene Targeting Frequency as a Function of the Extent of Homolgy between the Targeting Vector and the Target Locus," pp. 3365-3371.

*NATURE GENETICS, Vol. 20, 1998, Zhang, Y., et al., "A new logic for DNA engineering using recombination in *Escherichia coli*, " pp. 123-128.

*NUCLEIC ACIDS RESEARCH, Vol. 27, 1999, Angrand, P., et al., "Simplified generation of targeting constructs using ET recombination," pp. 16(e).

*NUCLEIC ACIDS RESEARCH, Vol. 27, 1999, Muyrers, J.P., et al., "Rapid modification of bacterial artificial chromosomes by ET-recombination," pp. 1555-1557.

*GENE THERAPY, Vol. 6, 1999, Narayanan, K. et al., "Efficient and precise engineering of a 200kb β -globin human/bacterial artificial chromosome in *E. coli* DH10B using an inducible homologous recombination system," pp. 442-447.

*GENOMICS, Vol. 64, 1999, Hill, F., et al., "BAC Trimming: Minimizing Clone Overlaps," pp. 111-113.

*NATURE BIOTECHNOLOGY, Vol. 15, 1997, Yang, X, et al., "Homologous recombination based modification in *Escherichia coli* and germline transmission in transgenic mice of a bacterial artificial chromosome," pp. 859-865.

*PROC. NATL. ACAD. SCI. USA, Vol. 97, 2000, Yu, D., et al.,
"An efficient recombination system for chromosome
engineering in *Escherichia coli*," pp. 5978-5983.

*PROC. NATL. ACAD. SCI. USA, Vol. 91, 1994, Hall, S. D, and
Kolodner, R.D., "Homologous pairing and strand exchange
promoted by the *Escherichia coli* RecT protein," pp. 3205-3209.

*GENE, Vol. 138, 1994, Kusano, K., et al., "Involvement of
RecE and RecT annealing protein in DNA double-stranded
break repair by homologous recombination," pp. 17-25.

*SCIENCE, Vol. 277, 1997, Kovall, R, and Matthews, B.W.,
"Toroidal Structure of λ -Exonuclease," pp. 1824-1827.

*COLD SPRINGS HARB SYMP QUANT BIOL, Vol. 49, 1984,
Clark, A.J., et al., "Genes of the RecE and RecF Pathways of
Conjugational Recombination in *Escherichia coli*," pp. 453-462.

*J BIOL CHEM, Vol. 273, 1998, Noirot, P., and Kolodner, R.D.,
"DNA Strand Invasion Promoted by *Escherichia coli* RecT
Protein," pp. 12274-80.

*J MOL BIOL, Vol. 254, 1995, Thresher, et al., "Electron
Microscopic Visualization of RecT Protein and its Complexes with
DNA,"pp. 364-371.

*MOLECULAR MICROBIOLOGY, Vol. 11, 1994, Kolodner, et
al., "Homologous pairing proteins encoded by the *Escherichia*
coli *recE* and *recT* genes," p. 23-30.

*JOURNAL OF BACTERIOLOGY, Vol. 175, 1993, Hall, S.D., et al., "Identification and Characterization of the *Escherichia coli* RecT Protein, a Protein Encoded by the *recE* Region That Promotes Renaturation of Homologous Single-Stranded DNA," pp. 277-287.

*JOURNAL OF BACTERIOLOGY, Vol. 173, 1991, Murphy, K.C., " λ Gam Protein Inhibits the Helicase and χ -Stimulated Recombination Activities of *Escherichia coli* RecBCD Enzyme," pp. 5808-5821.

*JOURNAL OF BACTERIOLOGY, Vol. 170, 1988, Poteete, A.R., and Fenton, A.C., "Modulation of *Escherichia coli* RecBCD Activity by the Bacteriophage λ Gam and P22 Abc Functions," pp. 2012-2021.

*ANNU REV GENET, Vol. 28, 1994, Myers, R.S., and Stahl, F.W., " χ AND THE RecBC D ENZYMEN OF *ESCHERICHIA COLI*," pp. 49-70.

*THE JOURNAL OF BIOLOGICAL CHEMISTRY, Vol. 259. 1984, Abremski K., and Hoess, R., "Bacteriophage P1 Site-specific Recombination-PURIFICATION AND PROPERTIES OF THE Cre RECOMBINASE PROTEIN," pp. 1509-1514.

*CELL, Vol. 40, 1985, Andrews, B.J., et al., "The FLP Recombinase of the 2 μ Circle DNA of Yeast: Interaction with Its Target Sequences," p. 795-803.

*COLD SPRING HARB SYMP QUANT BIOL, Vol. 49, Meyer-Leon, L., et al., "Site-specific Genetic Recombination Promoted by the FLP Protein of the Yeast 2-micron Plasmid *In Vitro*," pp. 797-804.

*PROC NATL ACAD SCI USA, Vol. 80, 1983, Cox, M.M., "The FLP protein of the yeast 2- μ m plasmid: Expression of a eukaryotic genetic recombination system in *Escherichia coli*," pp. 4223-4227.

*CURR OPIN BIOTECHNOL, Vol. 9, 1998, Lie, Y.S., and Petropoulos, C.J., "Advances in quantitative PCR technology: 5' nuclease assays," pp. 43-48.

*EUR J CHEM, Vol. 6, 2000, Tan, W., et al., "Molecular Beacons: A Novel DNA Probe for Nucleic Acid and Protein," pp. 1107-1111.

*HUM GENET, Vol. 96, 1995, Laan, M., et al., "Solid-phase minisequencing confirmed by FISH analysis in determination of gene copy number," pp. 275-280.

*TRENDS IN GENETICS, Vol. 13, 1997, Forozan, F., et al., "Genome screening by comparative genomic hybridization," pp. 405-409.

*JOURNAL OF CELLULAR BIOCHEMISTRY, Vol. 17G, 1993, Thompson, C.T., and Gray, J.W., "Cytogenetic Profiling Using Fluorescence *In Situ* Hybridization (FISH) and Comparative Genomic Hybridization (CGH)," pp. 139-143.

_____*AMERICAN JOURNAL OF PATHOLOGY, Vol. 145, 1994,
Houldsworth, J, and Chaganti, R.S.K., "Comparative
Genomic Hybridization: An Overview," p. 1253-1260.

_____*NATURE GENETICS, Vol. 19, 1998, Lizardi, P.M., et al.,
"Mutation detection and single-molecule counting using
isothermal rolling-circle amplification," pp. 225-232.

_____*NUCLEIC ACIDS RESEARCH, Vol. 27, 1999, Mitra, R.D., and
Church, G.M., "In situ localized amplification and contact
replication of many individual DNA molecules," pp. e34.

_____*NUCLEIC ACIDS RESEARCH, Vol. 25, No. 14, 1997, Bethke, Bruce
And Sauer, Brian, "Segmental genomic replacement by Cre-
Mediated recombination: genotoxic stress activation of the p53
promoter in single-copy transformants", pp. 2828-2834.

_____*MOLECULAR IMMUNOLOGY, Vol. 33, No. 17/18, 1996,
Shigeharu Fujieda, et al., "Direct Evidence That $\gamma 1$ And $\gamma 3$
Switching In Human B Cells Is Interleukin-10 Dependent", pp.
1335-1343.

_____*EUR. J. IMMUNOL., Vol. 28, 1998, Brain B. Haines and Peter H.
Brodeur, "Accessibility changes across the mouse Igh-V locus
during B cell development", pp. 4228-4235

_____*NATURE GENETICS, Vol. 20, 1998, Herault, Yann, et al.,
"Engineering chromosomes in mice through targeted meiotic
recombination (TAMERE)", pp. 381-384.

- _____
NUCLEIC ACIDS RESEARCH, Vol. 14, No. 5, 1986, Hoess, Ronald H., et al., "The role of the *loxP* spacer region in PI site-specific recombination", pp. 2287-2300.
- _____
EUR. J. IMMUNOL, Vol. 6, 1976, G. Kohler and C Milstein, "Derivation of specific antibody-producing tissue culture and tumor lines by cell fusion", pp. 511-519.
- _____
ANALYTICAL BIOCHEMISTRY, Vol. 290, 2001, Andreas F. Kolb, "Selection-Marker-Free Modification of the Murine β -Casein Gene Using a *lox2722* Site", pp. 260-271.
- _____
CURRENT OPINION IN BIOTECHNOLOGY, Vol. 9, 1998, Yolanda S. Lie and Christos J. Petropoulos, "Advances in quantitative PCR technology: 5' nuclease assays", pp. 43-48.
- _____
THE JOURNAL OF IMMUNOLOGY, 1998, Ong, Jane, et al., "3' IgH Enhancer Elements Shift Synergistic Interactions During B Cell Development", pp. 4896-4903.
- _____
EUR. J. IMMUNOL., Vol. 30, 2000, Pan, Qiang, et al., "Regulation of the promoter for human immunoglobulin $\gamma 3$ germ-line transcription and its interaction with the 3' α enhancer", pp. 1019-1029.
- _____
MOLECULAR AND CELLULAR BIOLOGY, Vol. 19, No. 10, October 1999, Ronai, Diana, et al., "Variegated Expression of the Endogenous Immunoglobulin Heavy-Chain Gene in the Absence of the Intronic Locus Control Region", pp. 7031-7040.

- ____ PNAS, Vol. 97, No. 2, January 18, 2000, Tomizuka, Kazuma, et al., "Double trans-chromosomal mice: Maintenance of two individual human chromosome fragments containing Ig heavy and κ loci and expression of fully human antibodies", pp. 722-727.
- ____ FACULTY OF BIOLOGY, University of Konstanz, Germany, 1999, Willers, Jörg, et al., "Apparent Trans-Chromosomal Antibody Class Switch in Mice Bearing an Igh^{α} μ -chain Transgene on an Igh^b Genetic Background", pp. 150-164.
- ____ NATURE BIOTECHNOLOGY, Vol. 15, September 1997, Yang, Xiangdong W. , et al., "Homologous recombination based modification in *Escherichia coli* and germline transmission in transgenic mice of a bacterial artificial chromosome", (sic) pp. 859-865.

* Items with an asterisk were submitted in parent applicatin USSN 09/732,234 on June 18, 2001.

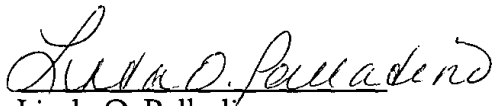
Reg 780D
USSN 10/076,840
Information Disclosure Statement
Murphy, et al.

EXAMINER
CONSIDERED

DATE

EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Respectfully submitted,

By: 
Linda O. Palladino
Reg. No. 45,636
Patent Agent for Applicants
Gail M. Kempler
Reg. No. 32,143
Joseph M. Sorrentino
Reg. No. 32,598
Laura J. Fischer
Reg. No. 50,420
Attorneys for Applicants
Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, New York 10591
(914) 345-7400